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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.

EXAMINER	
ART UNIT	PAPER NUMBER

C 1

DATE MAILED:

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 09/224,683	Applicant(s) ZSEBO ET AL.	
	Examiner Bridget E. Bunner	Art Unit 1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 May 2001*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *71-114* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *71-114* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a)☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____.
4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

The examiner of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1647, Examiner Bridget E. Bunner.

Continued Prosecution Application

The request filed on 17 May 2001 for a Continued Prosecution Application (CPA) under 37 CFR 1.53(d) based on parent Application No. 09/224,683 filed 31 December 1998 is acceptable and a CPA has been established. An action on the CPA follows.

Claims 71-114 are under consideration in the instant application.

Double Patenting

1. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 71-114 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 3-5, 8-9, 11-12, and 18-19 of U.S. Patent No. 6,204,363 in view of Remington's Pharmaceuticals Manual and Groopman et al. (N Engl J Med 321(21): 1449-1459, 1989). Although the conflicting claims are not identical, they are not patentably distinct from each other because both sets of claims are drawn to a polypeptide comprising the amino acid sequence 1-162, 1-164, and 1-165 as set forth in Figure 15C, wherein

the polypeptide optionally consists of an N-terminal methionine. The claims also recite a polypeptide comprising the amino acid 1-100, 1-110, 1-120, 1-123, 1-127, 1-130, 1-133, 1-137, 1-141, 1-156, 1-180, 1-185, 1-188, 1-189, 1-248, 2-164, 5-164, 11-164 as set forth in Figure 42A-C, wherein the polypeptide optionally consists of an N-terminal methionine. Further, the claims recite a polypeptide comprising the amino acid sequence 1-152, 1-157, 1-160, 1-161, and 1-220 as set forth in Figure 44A-D, wherein the polypeptide optionally consists of an N-terminal methionine. The various means of formulation and delivery of the composition are well known in the art, and one skilled in the art would have found it obvious to prepare the SCF composition in a manner consistent with the well known teaching of the Remington's Pharmaceuticals Manual. Furthermore, it would have also been *prima facie* obvious to admix the SCF polypeptides with other cytokines for the advantage of achieving an additive or synergistic effect. It is also well known in the art that many cytokines possess the same, similar, or over-lapping biological activities, and further known that combination therapies with one or more cytokines improves therapeutic effects. For example, Groopman et al. report that erythropoietin (EPO) stimulates the differentiation of primitive erythroid progenitors (pg 1450, col 2). Further, interleukin- (IL) 3 and GM-CSF have overlapping and synergistic activities, although IL-3 is more effective in stimulating early multipotent progenitors. The effects of IL-3 and GM-CSF on the survival and differentiation of early progenitors are enhanced by other cytokines, such as IL-1 and IL-6 (pg 1451, col 1; Table 1). Groopman et al. also state that "combinations of hematopoietic growth factors are likely to be an effective way to stimulate hematopoiesis broadly *in vivo*" (pg 1451, pp 1). Therefore, the instant claims reciting the combination of SCF

polypeptides with other cytokines is not patentably distinct over the issued claims in U.S. patent 6,204,363 in view of Remington's Pharmaceuticals Manual and Groopman et al.

Sequence Compliance

2. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825. *Specifically, the claims recite figure numbers rather than sequence identifiers.* Applicant must comply with the requirements of the sequence rules (37 CFR 1.821 - 1.825).

Drawings

3. This application has been filed with informal drawings which are acceptable for examination purposes only. Formal drawings will be required when the application is allowed.

Specification

4. The disclosure is objected to because of the following informalities:

4a. An updated status of the parent nonprovisional applications should be included in the first sentence of the specification.

4b. The first line of the specification does not claim priority to Application No. 07/684,535 and therefore is not in agreement with the Declaration of 15 March 1999.

4c. The Brief Description of the Drawings fails to refer to Figures 24A-24B; Figures 29A-29B; Figures 30A-30B; Figures 42A, 42B, 42C, 42D; Figures 44A, 44B, 44C; Figures 56A, 56B; Figures 70A, 70B.

4d. The specification is replete with references to U.S. patent Application Nos. The specification should include an updated status of these applications. For example, see pg 24 and 182.

Appropriate correction is required.

Claim Objections

5. Claim 104 is objected to because of the following informalities: There is a "." missing at the end of the claim. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 71-114 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a composition which comprises an effective amount of *human* stem cell factor (SCF) polypeptide and one or more cytokines in a pharmaceutically acceptable carrier wherein the SCF composition enhances hematopoiesis, does not reasonably provide enablement for a composition which comprises a therapeutically effective amount of SCF or biologically active fragment or analog thereof and one or more cytokines in a pharmaceutically acceptable carrier wherein the composition is effective to treat hematopoietic disorders, epithelial cell disorders, stromal cell disorders, neural disorders, pigmentation disorders, and germ cell disorders. Further, the specification, while being enabling for the SCF polypeptide consisting of the amino acid sequence of 1-162, 1-164, 1-165 of SEQ ID NO: 46; 1-130, 1-137, 1-248, 2-164, 5-164, 11-164 of SEQ ID NO: 61; and 1-220 of SEQ ID NO: 63, does

not reasonably provide enablement for the SCF polypeptide consisting of the amino acid sequence as set out as 1-100, 1-110, 1-120, 1-123, 1-127, 1-133, 1-141, 1-145, 1-148, 1-152, 1-156, 1-157, 1-158, 1-159, 1-160, 1-161, 1-163, 1-166, 1-168, 1-173, 1-178, 1-180, 1-183, 1-185, 1-188, 1-189 as set out in Figures 42A-C and 44A-C. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The specification teaches that "the present invention provides purified and isolated naturally-occurring SCF...as well as non-naturally occurring polypeptides having a primary structural conformation (i.e., continuous sequence of amino acid residues) and glycosylation sufficiently duplicative of that of naturally occurring stem cell factor to allow possession of a hematopoietic biological activity of naturally occurring SCF. Such polypeptides include derivatives and analogs" (pg 20, lines 27-36; pg 21, lines 1-2). The specification also discloses that analogs and derivatives of SCF share at least one of the biological properties of SCF but may differ in others (pg 22, lines 2-4). However, the specification does not disclose methods or examples that show how to use "biologically active" fragments or that describe the specific activity associated with all fragments.

Further, the specification does not teach all "analogs" or variants of the SCF polypeptide of the instant application. The specification only teaches that the human SCF polypeptide, particularly fragments comprising amino acids 1-130, 1-137, 1-162, 1-164, 1-165, 1-220, 1-248, 2-164, 5-164, and 11-164 of SEQ ID NOs: 46, 61, and 63, enhance the proliferation and differentiation of bone marrow progenitor cells (pg 108-114, 170-178, 185). The specification does not disclose any methods or working examples to demonstrate that human SCF fragments

comprising amino acids 1-100, 1-110, 1-120, 1-123, 1-127, 1-133, 1-141, 1-145, 1-148, 1-152, 1-156, 1-157, 1-158, 1-159, 1-160, 1-161, 1-163, 1-166, 1-168, 1-173, 1-178, 1-180, 1-183, 1-185, 1-188, 1-189 of SEQ ID NOs: 46, 61, and 63 or any variants or "analogs" have any specific activity. A large quantity of experimentation would be required of the skilled artisan to determine any structural or functional characteristics of the SCF fragments comprising amino acids 1-100, 1-110, 1-120, 1-123, 1-127, 1-133, 1-141, 1-145, 1-148, 1-152, 1-156, 1-157, 1-158, 1-159, 1-160, 1-161, 1-163, 1-166, 1-168, 1-173, 1-178, 1-180, 1-183, 1-185, 1-188, 1-189 of SEQ ID NOs: 46, 61, and 63.

The problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex. While it is known that many amino acid substitutions are generally possible in any given protein the positions within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of success are limited. Certain positions in the sequence are critical to the protein's structure/function relationship, e.g. such as various sites or regions directly involved in binding, activity and in providing the correct three-dimensional spatial orientation of binding and active sites. These or other regions may also be critical determinants of antigenicity. These regions can tolerate only relatively conservative substitutions or no substitutions (see Wells, 1990, Biochemistry 29:8509-8517; Ngo et al., 1994, The Protein Folding Problem and Tertiary Structure Prediction, pp. 492-495). However, Applicant has provided little or no guidance beyond the mere presentation of sequence data to enable one of ordinary skill in the art to determine, without undue experimentation, the positions in the protein which are tolerant to change (e.g. such as by amino acid substitutions or deletions), and the

nature and extent of changes that can be made in these positions. Although the specification outlines art-recognized procedures for producing and screening for active muteins, this is not adequate guidance as to the nature of active derivatives that may be constructed, but is merely an invitation to the artisan to use the current invention as a starting point for further experimentation. Even if an active or binding site were identified in the specification, they may not be sufficient, as the ordinary artisan would immediately recognize that an active or binding site must assume the proper three-dimensional configuration to be active, which conformation is dependent upon surrounding residues; therefore substitution of non-essential residues can often destroy activity. The art recognizes that function cannot be predicted from structure alone (Bork, 2000, Genome Research 10:398-400; Skolnick et al., 2000, Trends in Biotech. 18(1):34-39, especially p. 36 at Box 2; Doerks et al., 1998, Trends in Genetics 14:248-250; Smith et al., 1997, Nature Biotechnology 15:1222-1223; Brenner, 1999, Trends in Genetics 15:132-133; Bork et al., 1996, Trends in Genetics 12:425-427).

Additionally, the specification does not disclose any methods or working examples of administering any human SCF polypeptide fragment-cytokine composition to treat a hematopoietic disorder, an epithelial disorder, a stromal cell disorder, a neural disorder, a pigmentation disorder, or a germ cell disorder. Undue experimentation would be required of one skilled in the art to determine the efficacy of treatment of numerous diseases after administration of the SCF polypeptide-cytokine composition. A large quantity of experimentation would also be necessary to determine the quantity, frequency, and duration of the treatment.

Due to the large quantity of experimentation necessary to generate the "biologically active" derivatives or "analogs" recited in the claims, to determine the specific activity of a

polypeptide fragment, and to determine the efficacy of treatment, the lack of direction/guidance presented in the specification regarding which structural features that are required in order to provide activity, the absence of working examples directed to same, the complex nature of the invention, the state of the prior art which establishes the unpredictability of the effects of mutation on protein structure and function, and the breadth of the claims which fail to recite any structural or functional limitations, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

7. Claims 71-114 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 71-114 recite a therapeutically effective amount of SCF or biologically active fragment or analog thereof and one or more cytokines in a pharmaceutically acceptable carrier wherein the composition is effective to treat hematopoietic disorders, epithelial cell disorders, stromal cell disorders, neural disorders, pigmentation disorders, and germ cell disorders. The claims also recite that the SCF polypeptide consists of the amino acid sequence as set out as 1-100, 1-110, 1-120, 1-123, 1-127, 1-133, 1-141, 1-145, 1-148, 1-152, 1-156, 1-157, 1-158, 1-159, 1-160, 1-161, 1-163, 1-166, 1-168, 1-173, 1-178, 1-180, 1-183, 1-185, 1-188, 1-189 as set out in Figures 42A-C and 44A-C.

The specification teaches a human SCF polypeptide, particularly fragments comprising amino acids 1-130, 1-137, 1-162, 1-164, 1-165, 1-220, 1-248, 2-164, 5-164, and 11-164 of SEQ

ID NOs: 46, 61, and 63, that enhance the proliferation and differentiation of bone marrow progenitor cells (pg 108-114, 170-178, 185). However, the specification does not specifically point to or discuss human SCF fragments comprising amino acids 1-100, 1-110, 1-120, 1-123, 1-127, 1-133, 1-141, 1-145, 1-148, 1-152, 1-156, 1-157, 1-158, 1-159, 1-160, 1-161, 1-163, 1-166, 1-168, 1-173, 1-178, 1-180, 1-183, 1-185, 1-188, 1-189 of SEQ ID NOs: 46, 61, and 63 or any variants or "analogs". The specification also does not teach functional or structural characteristics of the polynucleotides in the context of a cell or organism. The description of ten specific SCF polypeptide fragments that enhance hematopoiesis is not adequate written description of an entire genus of functionally equivalent polynucleotides and polypeptides which incorporate all biologically active fragments and analogs of SCF.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed*" (See page 1117). The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed" (See *Vas-Cath* at page 1116).

With the exception of the sequences referred to above, the skilled artisan cannot envision the detailed chemical structure of the encompassed polynucleotides, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The nucleic acid

itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Therefore, only a composition comprising human SCF polypeptide fragments comprising amino acids 1-130, 1-137, 1-162, 1-164, 1-165, 1-220, 1-248, 2-164, 5-164, and 11-164 of SEQ ID NOs: 46, 61, and 63, but not the full breadth of the claim meets the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

35 USC § 112, second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

8. Claims 71-114 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

9. Regarding claims 71-114, the phrase "thereof" renders the claims indefinite because it is unclear whether "thereof" refers to the entire polypeptide or variants and fragments of the polypeptide.

10. Regarding claims 91-102, the acronyms "IL-1, IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-8, IL-9, IL-10, IL-11, IL-12, EPO, G-CSF, GM-CSF, CSF-1, IGF-1, and LIF" render the claims vague and indefinite. Abbreviations should be spelled out in all independent claims for clarity.

Conclusion

No claims are allowable.

The art made of record and not relied upon is considered pertinent to applicant's disclosure:

Besmer et al. U.S. patent 5,767,074

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bridget E. Bunner whose telephone number is (703) 305-7148. The examiner can normally be reached on 8:00-5:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor. Gary Kunz can be reached on (703) 308-4623. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 308-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

BEB
Art Unit 1647
July 12, 2001

Elizabeth C Kemmerer

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